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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/920,272	08/22/1997	FREDA MILLER	CIBT-P01-120	8297
21559	7590	05/17/2004	EXAMINER	
CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			MURPHY, JOSEPH F	
			ART UNIT	PAPER NUMBER

1646

DATE MAILED: 05/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<p align="center">Office Action Summary</p>	Application No. 08/920,272	Applicant(s) MILLER ET AL.	
	Examiner Joseph F Murphy	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 32,33,41,42,49-52 and 54-58 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 32-33, 41-42, 49-52, 54-58 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Formal Matters

Claims 32-33, 41-42, 49-52, 54-58 are pending and under consideration.

Response to Amendment and Arguments

Applicant's amendment and arguments filed 3/1/2004 have been fully considered but they are not persuasive, for the reasons set forth below.

New issues raised by Applicant's amendment filed 3/1/2004 are also set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 51 is vague and indefinite because the claim as amended lacks a transitional phrase, and thus the metes and bounds of the claim cannot be determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 32-33, 49-52, 54-57, 59-60 stand rejected under 35 U.S.C. 102(a) as being anticipated by Sosnowski et al. (1995) for reasons of record set forth in the Office Action of 8/26/2003.

The rejection of record set forth that Sosnowski et al. (page 38, column 1, second paragraph to column 2, first paragraph) teaches the establishment in primary culture of olfactory epithelium isolated from adult mouse. Based upon immunoreactivity (page 45, column 1, fourth paragraph) to antibodies specific for intermediate filament proteins, the cells present in cultures were identified as neurons, glia or epithelial cells. The claims are directed to compositions of cells comprising neural stem cells with these properties. The claimed cellular compositions comprise multipotent stem cells with the recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. Additionally, the composition of cells as taught by Sosnowski would be inherent to comprise cells that are capable of forming non-adherent clusters. It is an inherent property of multipotent neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner. Thus, given the inherent properties of the multipotent neural stem cells derived from peripheral tissue, and the lack of a recitation of the purity of the stem cells, claims 50-52, 54-57, 59-60, are anticipated.

Claim 49 is a product by process claim, and claims 32-33, 56-57, 59-60 depend from claim 49. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. In re Thorpe, 227 USPQ 964 (Fed. Cir. 1985). In addition, it has

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been established by the courts that when a product (i.e. mammalian neural stem cells) inherently possesses a characteristic of that product (see e.g. *Ex parte Gray*, 10 USPQ2D, 1922; *In re Best*, 195 USPQ 430), that “[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency’ under 35 U.S.C. 102, on prima facie obviousness’ under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted].” The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983). In the instant case, the claimed cellular compositions comprise multipotent stem cells with several recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. Furthermore, it is an inherent property of mammalian neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner, therefore claims 32-33, 49, 56-57, 59-60 are anticipated.

Applicant has amended the claims to recite the limitation wherein the composition comprises an isolated population of neural stem cells of a mammal, and Applicant argues that at

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no time did the cultures described by Sosnowski consist of isolated stem cells. Applicant further points out that the Sosnowski reference acknowledges that the tissue included mostly olfactory epithelium, and also included respiratory epithelium, lamina propria etc. However, the claim as written is directed to a composition which comprises, amongst other things, neural stem cells. The term “comprising” is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim. Thus the use of the term “comprising” leaves “the claim open for the inclusion of unspecified ingredients even in major amounts” (see MPEP 2111.03). The claim as written is thus anticipated by the Sosnowski reference since the Sosnowski reference teaches a composition comprising neural stem cells of a mammal.

Claims 32-33, 49-52, 54-57, 59-60 stand rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 5,318,907 (Ronnette et al.) for reasons of record set forth in the Office Action of 8/26/2003.

The rejection of record set forth that Ronnette et al. (column 6 line 58 to column 7 line 46) discloses the isolation of cells from the olfactory epithelium of neonatal rats, and their establishment in primary culture. The presence of both neurons and glial cells is demonstrated through immunoreactivity with antibodies specific for neurons (anti-neuron-specific enolase) and glial cells (anti-glial fibrillary acidic protein) (column 8, lines 34-47). The development in culture of neuronal cells indicates the presence of neural stem cells and neural progenitor cells. The instant claims are directed to compositions of cells comprising neural stem cells with these properties. The claimed cellular compositions comprise multipotent stem cells with several recited properties, but may also comprise neural stem cells with different properties, since there

is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. In the '907 patent, the presence in culture of glial cells, together with the presence of neurons meets the limitations for a multipotent cell. Thus the cells disclosed in the '907 patent meet the limitations set forth in the claims for an isolated composition of neural stem cells of a mammal (see column 2, lines 41-45). Additionally, the composition of cells as disclosed in the '907 patent would be inherent to comprise cells which are capable of forming non-adherent clusters. It is an inherent property of multipotent neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner. Thus, given the inherent properties of the multipotent neural stem cells derived from peripheral tissue, and the lack of a recitation of the purity of the stem cells, the claims are anticipated. Furthermore, it would be an inherent property of the composition of cells as disclosed in the '907 patent to comprise cells which are capable of forming non-adherent clusters. It is an inherent property of multipotent neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner. Thus, given the inherent properties of the multipotent neural stem cells derived from peripheral tissue, and the lack of a recitation of the purity of the stem cells, claims 50-52, 54-57, 59-60, are anticipated.

Claim 49 is a product by process claim, and claims 32-33, 56-57, 59-60 depend from claim 49. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985). In addition, it has

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been established by the courts that when a product (i.e. mammalian neural stem cells) inherently possesses a characteristic of that product (see e.g. *Ex parte Gray*, 10 USPQ2D, 1922; *In re Best*, 195 USPQ 430), that “[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency’ under 35 U.S.C. 102, on prima facie obviousness’ under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted].” The burden of proof is similar to that required with respect to product-by-process claims. *In re Fitzgerald*, 619 F.2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)).

Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983). In the instant case, the claimed cellular compositions comprise multipotent stem cells with several recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. Furthermore, it is an inherent property of mammalian neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner, therefore claims 32-33, 56-57, 59-60 are anticipated.

Applicant has amended the claims to recite the limitation wherein the composition comprises an isolated population of neural stem cells of a mammal, and Applicant argues that at

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no time did the cultures described by the '907 patent consist of isolated stem cells. Applicant further points out that the '907 patent acknowledges that the tissue included mostly olfactory epithelium, and also included respiratory epithelium, lamina propria etc. However, the claim as written is directed to a composition which comprises, amongst other things, neural stem cells. The term "comprising" is a term of art used in claim language which means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim. Thus the use of the term "comprising" leaves "the claim open for the inclusion of unspecified ingredients even in major amounts" (see MPEP 2111.03). Since the '907 patent discloses a composition comprising neural stem cells of a mammal, the claims are anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 32-33, 41-42, 49-52, 54-60 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sosnowski et al (1995), in view of U.S. Patent No. 5,824,489 (Anderson et al.) for reasons of record set forth in the Office Action of 12/4/2002 and 8/26/2003.

The rejection of record set forth that Sosnowski et al.(page 38, column 1, second paragraph to column 2, first paragraph) teaches a primary culture of olfactory epithelium isolated from adult mouse. Based upon immunoreactivity (page 45, column 1, fourth paragraph) to antibodies specific for intermediate filament proteins, the cells present in cultures were identified

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as neurons, glia or epithelial cells. Thus, Sosnowski teaches progenitor cells isolated from peripheral tissue, in this instance olfactory epithelium, of a postnatal mammal. The cells isolated by Sosnowski et al. have been shown to be multipotent, due to the presence in culture of several cell types. Sosnowski et al. teaches that the cultures established from regenerating olfactory tissue after chemical insult exhibited a range of neuronal yields (page 47, column 1, third paragraph). Cellular components of the cultures produced by Sosnowski et al. tested positive for keratin, as well as 200 kD and 160 kD neurofilament proteins, indicating the establishment of mixed olfactory epithelial cultures containing olfactory neurons (page 46, column 1, first paragraph). The cells comprising the composition of Sosnowski et al. were isolated from peripheral tissue, i.e. olfactory epithelium, in a fashion similar to the cells claimed in the instant application. The cells in the composition taught by Sosnowski et al. differentiate to produce neuronal cells, as do the cells of the instant application. The cells in the composition of Sosnowski et al. can be transplanted into the CNS of a mammal, as can the cells of the instant application.

The cells of Sosnowski et al. do not express nestin or are transfected with a heterologous gene. The '489 patent discloses multipotent neural stem cells can be derived from neural epithelial tissue from the brain and/or spinal cord of the adult central nervous system or neural epithelial tissue which may be present in tissues comprising the peripheral nervous system. In addition, the '489 patent discloses that such multipotent neural stem cells may be derived from other tissues such as lung, bone and the like (column 5, lines 40-47). The cells disclosed in the '489 patent express nestin (column 6, lines 1-5). The '489 patent discloses that the cells may be transfected with a vector (column 3, lines 59-63) and that mammalian neural crest stem cells may

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be isolated from human tissues (column 4, lines 54-58). Therefore it would have been obvious to one of skill in the art at the time the invention was made to make a population of neural stem cells from a mammal, including humans, from peripheral tissue, wherein the neural stem cell expresses nestin. The motivation is provided in the '489 patent which discloses that the ability to isolate and grow mammalian neural crest stem cells in vitro allows for the possibility of using said stem cells to treat peripheral neurological disorders in mammals, particularly humans.

Applicant argues that there was no motivation to combine the teachings of Sosnowski and Anderson because not all multipotent stem cells are nestin positive. However, the '489 patent discloses that multipotent neural stem cells may be derived from various tissues, including, inter alia the peripheral nervous system (column 5, lines 39-47). The '489 patent further discloses that the multipotent neural stem cells may also be characterized by the expression of nestin (column 6, lines 1-5). The disclosure of the '489 patent thus teaches that nestin positive multipotent neural stem cells may be derived from tissues other than neural crest, specifically from the peripheral nervous system. The Sosnowski reference teaches multipotent cells derived from the peripheral tissues of a mammal, thus it would have been obvious at the time the invention was made to produce the nestin positive multipotent neural stem cells as taught in the '489 patent by using the peripheral olfactory tissue as taught by the Sosnowski reference, since the Sosnowski reference teaches the unique capacity of the olfactory epithelium to remain mitotically active throughout a mammals life, and that the multipotent cells derived from olfactory epithelium could be harvested, grown and autotransplanted.

Applicant further argues that the combination of the Sosnowski reference with the '489 patent fails to teach every element of the claims because they do not teach non-adherent clusters

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of stem cells, they do not teach that the stem cells are capable of differentiating into dopaminergic neurons, and they do not teach that the stem cells are GAD positive. Applicant additionally argues that the combination of the Sosnowski reference with the '489 patent fails to teach every element of the claims because they do not teach cells which are self-renewing in an EGF independent manner. However, the claims are directed to compositions of cells comprising neural stem cells with these properties. The claimed cellular compositions comprise multipotent stem cells with the recited properties, but may also comprise neural stem cells with different properties, since there is no limitation for the relative purity of the neural stem cells with the properties as set forth in the claims. Additionally, the composition of cells as taught by Sosnowski in view of the '489 patent would be expected to comprise cells which are capable of forming non-adherent clusters. It is an expected property of multipotent neural stem cells that they are GAD positive, are capable of differentiating into dopaminergic neurons or cells expressing GFAP, or cells which are self-renewing in an EGF independent manner. Thus, given the expected properties of the multipotent neural stem cells derived from peripheral tissue, and the lack of a recitation of the purity of the stem cells, the claims are unpatentable.

Applicant further argues that the Examiner has used hindsight to combine the references. However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272-0871.

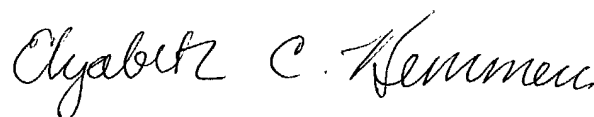
The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
May 5, 2004



ELIZABETH KEMMERER
PRIMARY EXAMINER